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EXAMINER	
SKELDING, ZACHARY S	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/568,745	IDENO ET AL.	
	Examiner	Art Unit	
	ZACHARY SKELDING	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-9 and 13-24* is/are pending in the application.

4a) Of the above claim(s) *14,17-19 and 22-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-9,13,15,16,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2-3-11 and 2-24-11*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 7, 2010 has been entered.

   Claims 1-4, 6-9 and 13-24 are pending.

   Claims 1-4, 6-9, 13, 15, 16, 20 and 21 are under examination wherein the elected species of fibronectin fragment is SEQ ID NO: 13 and wherein the method includes a step of diluting a cell culture solution.

   Claims 14, 17-19 and 22-24 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected Group or species of invention.

2. The previous grounds of rejection can be found in the Office Action mailed July 12, 2010.

   The previous rejection under 35 U.S.C. § 112, 1st paragraph, written description, has been withdrawn in view of applicant's amendments to the claims.

   The previous rejection under 35 U.S.C. § 112, 1st paragraph, enablement, has been withdrawn upon further consideration. That said, a new rejection under 35 U.S.C. § 112, 1st paragraph, enablement maintaining the prior rejection and adding a new issue is put forth below.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

   > The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-4, 6-9, 13, 15, 16, 20 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

   A method for preparing a population of cytotoxic lymphocytes comprising

   obtaining peripheral mononuclear cells which have an ability to differentiate into cytotoxic lymphocytes,

culturing said peripheral mononuclear cells in a medium containing added IL-2 and further containing serum and plasma at a total concentration of 0% by volume or more and less than 5% by volume,

wherein said culturing is performed in the presence of a recombinant fibronectin fragment which is a polypeptide comprising at least any one of the amino acid sequences shown in SEQ ID NOs: 1 to 20 and 25 of the sequence listing, wherein said fibronectin fragment comprises a cell adhesion activity and/or a heparin binding activity,

and wherein a cytotoxic activity is enhanced or a high cytotoxic activity is maintained as compared to a cytotoxic activity of a cytotoxic lymphocyte prepared in the absence of the recombinant fibronectin fragment.

does not reasonably provide enablement for

A method for preparing a cytotoxic lymphocyte which method comprises the step of carrying out at least one step selected from the group consisting of induction from peripheral mononuclear cells or umbilical cord blood mononuclear cells which can be formed into the cytotoxic lymphocyte, maintenance of a cytotoxic lymphocyte and expansion of a cytotoxic lymphocyte, comprising-culturing the peripheral mononuclear cells or umbilical cord blood mononuclear cells which have an ability of differentiating into the lymphocyte with a medium containing serum and plasma at a total concentration 0f 0% by volume or more and less than 5% by volume, in the presence of a recombinant fibronectin fragment, a fragment thereof or a mixture thereof, which is a polypeptide comprising at least any one of the amino acid sequences shown in SEQ ID NOs: 1 to 20 and 25 of the sequence listing, wherein said fibronectin fragment comprises a cell adhesion activity and/or a heparin binding activity, and wherein a cytotoxic activity is enhanced or a high cytotoxic activity is maintained as compared to a cytotoxic activity of a cytotoxic lymphocyte prepared in the absence of the recombinant fibronectin fragment.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, in re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

"The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is,

the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)" The MPEP further states that physiological activity can be considered inherently unpredictable.

The instant claims are drawn to a method for preparing a cytotoxic lymphocyte which method comprises the step of carrying out at least one step selected from the group consisting of induction from peripheral mononuclear cells or **umbilical cord blood mononuclear cells** which can be formed into the cytotoxic lymphocyte, maintenance of a cytotoxic lymphocyte and expansion of a cytotoxic lymphocyte, comprising-culturing the peripheral mononuclear cells **or umbilical cord blood mononuclear** cells which have an ability of differentiating into the lymphocyte with a medium containing serum and plasma at a total concentration 0f 0% by volume or more and less than 5% by volume, in the presence of a recombinant fibronectin fragment, a fragment thereof or a mixture thereof, which is a polypeptide comprising at least any one of the amino acid sequences shown in SEQ ID NOs: 1 to 20 and 25 of the sequence listing, wherein said fibronectin fragment comprises a cell adhesion activity and/or a heparin binding activity, and wherein a cytotoxic activity is enhanced or a high cytotoxic activity is maintained as compared to a cytotoxic activity of a cytotoxic lymphocyte prepared in the absence of the recombinant fibronectin fragment.

As to the use of umbilical cord blood mononuclear cells in the claimed method, as put forth in the prior Office Action mailed July 12, 2010 at page 6, 1st paragraph,

"...while peripheral blood mononuclear cells are known to be a suitable precursor population for the differentiation of cytotoxic lymphocytes, including CTL and LAK cells (see Jung et al., 1987, J. Immunol. Vol. 139: 639-644, cited on an IDS), the use of other precursor cells for differentiation into a cytolytic lymphocyte population with fibronectin is unpredictable. For example, umbilical cord blood lymphocytes are different in phenotype and function from lymphocytes of normal adults, with cord blood lymphocytes displaying a functionally immature phenotype (see Lucivero et al., 1996, Int J. Clin. Lab Res. Vol. 26: 255-261, page 260 in particular, cited on an IDS). In fact, stimulants such as anti-CD3 fail to induce proliferation of cord blood lymphocytes (see page 260, in particular). Thus, differentiation of cord blood lymphocytes into a population of cells comprising enhanced cytolytic activity would be highly unpredictable..."

Applicant argues that based on the publication by Nelson et al., the ordinary artisan would have readily understood that cytotoxic lymphocytes could have been obtained using peripheral blood mononuclear cells or umbilical cord blood mononuclear cells.

Applicant's argument has been considered but has not been found convincing for the reasons put forth below.

Nelson teaches cord blood cells stimulated with anti-CD3 upregulate IL-2R. Luciverto also teaches cord blood cells stimulated with anti-CD3 upregulate IL-2R.

However, the instant claims are drawn to a method for **preparing a cytotoxic lymphocyte** which method comprises the step of carrying out at least one step selected from the group consisting of induction from peripheral mononuclear cells or **umbilical cord blood mononuclear cells** which can be formed into the cytotoxic lymphocyte, maintenance of a cytotoxic lymphocyte and expansion of a cytotoxic lymphocyte, comprising-culturing the peripheral mononuclear cells or **umbilical cord blood mononuclear cells** which have an ability of differentiating into the lymphocyte with a medium containing…**wherein a cytotoxic activity is enhanced or a high cytotoxic activity is maintained** as compared to a cytotoxic activity of a cytotoxic lymphocyte prepared in the absence of the recombinant fibronectin fragment.

Both Nelson and Luciverto teach cord blood T cells differ functionally from adult peripheral blood T cells.

For example, Nelson teach cord blood T cells fail to produce soluble IL-2R in response to anti-CD3 stimulation, which indicates that cord blood T cells might not be fully functional (see page 138, in particular).

Furthermore, as noted above, Luciverto teaches that cord blood T cells fail to proliferate in response to anti-CD3.

Thus, the state of the art is such that cord blood T cells appear to be not fully functional compared to adult peripheral blood T cells. Thus, producing cytotoxic lymphocytes from umbilical cord blood mononuclear cells would be a highly unpredictable endeavor. Applicant has not cited any evidence demonstrating that producing cytotoxic lymphocytes from umbilical cord blood mononuclear cells is routinely performed in the art, as is the case for adult peripheral mononuclear cells.

As to practicing the claimed method to its full breadth, it is noted that the method as currently claimed does not require the addition of IL-2 to the cell culture. Rather, the instant claims give their broadest reasonable interpretation consistent with the teachings of the instant specification encompass in their breadth methods where the peripheral blood mononuclear cells are cultured in a medium containing 0% to less than 5% serum, a recombinant fibronectin fragment and any cytokine. (see, e.g., pages 24-25 and 30-31 bridging paragraphs).

However, all of the working examples put forth in the instant specification include IL-2, and none exemplify practice of the claimed method in the absence of IL-2 with or without some other cytokine. Furthermore, the instant specification teaches the following on the page 4-5 bridging paragraph about the role of IL-2 in the claimed method:

"As described above, utilization of IL-2 is essential in the step of obtaining a cytotoxic lymphocyte, for instance, CTL, LAK cell, TIL or the like. The cell is further activated by binding of IL-2 to interleukin-2 receptor (IL-2R) on a cell surface. In addition, IL-2R has been known as an activation marker for a lymphocyte. From these viewpoints, it is important to improve IL-2R expression on the cell surface. In addition, in the induction of CTL, it is important to improve an efficiency for inducing a precursor cell of CTL subjected to stimulation by an antigen as CTL, i.e., to improve a proportion (ratio) of the CD8-positive cell in a group of cells after the induction."

Thus, it appears from the teachings of the instant specification that IL-2 is essential to the practice of the claimed method. A claim which omits matter disclosed to be essential to the invention as described in the specification or in other statements of record may be rejected under 35 U.S.C. 112, first paragraph, as not enabling. In re Mayhew, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

Moreover, the instant specification provides insufficient guidance for the skilled artisan to practice the claimed method in the absence of IL-2 with or without some other cytokine. Indeed, like the teachings of the instant specification the prior art indicates that the presence of IL-2 is required for the production of cytotoxic lymphocytes from peripheral mononuclear cells, and that other cytokines, in the absence of IL-2, have no ability to induce the production of cytotoxic lymphocytes from peripheral mononuclear cells (see, e.g., Gallagher et al., Clin. exp. Immunol. (1988) 74, 166-170 as well as Parhar et al., Eur Cytokine Netw. 1992 May-Jun;3(3):299-306, entire document for each, including Table 1 in Parhar). Thus, to practice the claimed method in the absence of IL-2 with or without some other cytokine the skilled artisan would first have to determine, without guidance from the instant specification, what other cytokines, and possibly some other unknown components must be added to the peripheral mononuclear cells cultured in a medium containing 0% to less than 5% serum and a recombinant fibronectin fragment to produce the claimed cytotoxic lymphocytes having an enhanced or high cytotoxic activity maintained as compared to a cytotoxic activity of a cytotoxic lymphocyte prepared in the absence of the recombinant fibronectin fragment, which is hardly a matter of routine experimentation.

In conclusion, the scope of the claims must bear a reasonable correlation with the scope of enablement. In re Fisher, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

As put forth in Rasmusson v. SmithKline Beecham Corp., 75 USPQ2d 1297-1303 (CAFC 2005), "[i]f mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to 'inventions' consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the 'inventor' would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

Similarly, a patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of Genentech, Inc, v. Novo Nordisk, 42 USPQ 2d 1001,(CAFC 1997), the court held: "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". Further, "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

The instant specification is not enabling because the skilled artisan cannot follow the guidance presented therein to practice the claims without first making a substantial inventive contribution, which is hardly a matter of routine experimentation.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-4, 6-9, 13, 15, 16, 20 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims recite: "A method for preparing a cytotoxic lymphocyte which method comprises the step of carrying out at least one step selected from the group consisting of induction from peripheral mononuclear cells or umbilical cord blood mononuclear cells which can be formed into the cytotoxic lymphocyte, maintenance of a cytotoxic lymphocyte and expansion of a cytotoxic lymphocyte, comprising culturing the peripheral mononuclear cells or umbilical cord blood mononuclear cells which have an ability of differentiating into the lymphocyte with a medium containing serum and plasma at a total concentration 0f 0% by volume or more and less than 5% by volume, in the presence of a recombinant fibronectin fragment, a fragment thereof or a mixture thereof, which is a polypeptide comprising at least any one of the amino acid sequences shown in SEQ ID NOs: 1 to 20 and 25 of the sequence listing, wherein said fibronectin fragment comprises a cell adhesion activity and/or a heparin binding activity, and wherein a cytotoxic activity is enhanced or a high cytotoxic activity is maintained as compared to a cytotoxic activity of a cytotoxic lymphocyte prepared in the absence of the recombinant fibronectin fragment."

One issue is that the meaning of the phrase in the claim preamble "induction from peripheral mononuclear cells or umbilical cord blood mononuclear cells which can be formed into the cytotoxic lymphocyte," and the similar phrase in the claim body "comprising culturing the peripheral mononuclear cells or umbilical cord blood mononuclear cells which have an ability of differentiating into the lymphocyte" is unclear on several levels. First, it is unclear if the phrases "which can be formed into the cytotoxic lymphocyte" / "which have an ability of differentiating into the lymphocyte" are referring to both the "peripheral mononuclear

cells" and the "umbilical cord blood mononuclear cells" or only to the "umbilical cord blood mononuclear cells." Secondly, the phrase "peripheral mononuclear cells" is often understood by the skilled artisan based on the context in which it is used. For example, B-cells, T-cells, NK cells and monocytes may each be described as "peripheral mononuclear cells" and referred to as such. On the other hand, the skilled artisan may describe, e.g., using leukapheresis to harvest bulk "peripheral mononuclear cells" from blood, in which case the phrase "peripheral mononuclear cells" is understood to refer to the collection of B-cells, T-cells, NK cells and monocytes found in blood.

Another issue is the relationship between the preamble of the claim and the body of the claim is unclear. The preamble recites "a method for preparing a cytotoxic lymphocyte which method comprises the step of carrying out at least one step selected from the group consisting of induction from peripheral mononuclear cells or umbilical cord blood mononuclear cells which can be formed into the cytotoxic lymphocyte, maintenance of a cytotoxic lymphocyte and expansion of a cytotoxic lymphocyte, comprising..." while the first step of the claim body recites "...culturing the peripheral mononuclear cells or umbilical cord blood mononuclear cells which have an ability of differentiating into the lymphocyte..."

While the language of the claim body "which have an ability of differentiating into the lymphocyte" is consistent with "induction from peripheral mononuclear cells or umbilical cord blood mononuclear cells which can be formed into the cytotoxic lymphocyte," the preamble seems to indicate that other sorts of endpoints are being reached: "maintenance of a cytotoxic lymphocyte" or "expansion of a cytotoxic lymphocyte." However, it is not clear how the steps of the claim body relate to the achievement of these other endpoints. For example, if a skilled artisan is attempting to practice "a method for preparing a cytotoxic lymphocyte which method comprises the step of carrying out...maintenance of a cytotoxic lymphocyte...comprising..." then to practice the claimed method must the skilled artisan perform a step of "culturing peripheral mononuclear cells or umbilical cord blood mononuclear cells which have an ability of differentiating into the lymphocyte with a medium containing serum and plasma..." or does practicing a method comprising a step of carrying out maintenance of a cytotoxic lymphocyte somehow require that the cells being cultured "peripheral mononuclear cells or umbilical cord blood mononuclear cells which have an ability of differentiating into the lymphocyte" are something other than bulk peripheral mononuclear cells or umbilical cord blood mononuclear cells, i.e., certain types of peripheral mononuclear cells or umbilical cord blood mononuclear cells which have a preexisting cytotoxic activity?

In sum, given the interdependence of the language used in the claim, and the issues outlined above, the metes and bounds of the claimed method would be unclear to the skilled artisan and thus it would not be possible for the skilled artisan to ascertain what activities would or would not infringe upon the instant claims should they become patented.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-4, 6-9, 13, 15 and 16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Frederick Darfler (WO 88/02774) in view of Ochoa et al. (Cancer Res. 1989 Feb 15;49(4):963-8), Cardarelli et al. (Cell Immunol. 1991 Jun;135(1):105-17) and Taguchi et al. (U.S. Patent 5,198,423), essentially for the reasons of record as put forth in the Office Action mailed July 12, 2010.

Applicant puts forth the following argument at page 11-12 bridging paragraph – page 12, 1st paragraph of their remarks filed October 7, 2010:

"Applicants submit that an ordinary artisan at the time of the invention could not have reasonably predicted from the cited references that incubating a recombinant fibronectin fragment with peripheral mononuclear cells or umbilical cord blood mononuclear cells in substantially serum-free medium, as described in the instant claims, would result in enhanced cytotoxicity or the maintenance of a high cytotoxic activity.

Cardarelli describes a native fibronectin. In contrast, the claimed method employs a recombinant fibronectin fragment. Moreover, Cardarelli does not teach that fibronectin enhances cytotoxicity, but only teaches that fibronectin enhances proliferation, see Cardarelli, which states that T cell proliferation is measured by determining the amount of 3H-thymidine uptake upon DNA synthesis of cells, see pages 107-108 of Cardarelli. In addition, Darfler's method describes using a compound for activating kinase C in order to obtain a serum-free medium, which has the equivalent function of a serum containing medium. However, kinase C activating compounds are not utilized in the claimed method. In view of the foregoing, an ordinary artisan could not have reasonably predicted that combining the serum-free medium of Darfler with a recombinant fibronectin fragment in the presence of peripheral mononuclear cells or umbilical cord blood mononuclear cells could have resulted in enhanced cytotoxicity or maintaining a high level of cytotoxicity."

Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed July 12, 2010.

First, arguments against the teachings of individual references, e.g., "Cardarelli describes a native fibronectin. In contrast, the claimed method employs a recombinant fibronectin fragment" cannot rebut a case of prima facie obviousness based on the combined reference teachings. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). see MPEP § 2145.

Second, regarding applicant's arguments about the teachings of Darfler, objective evidence teaches that the AIM-V serum-free medium used in applicant's working examples does contain a compound for activating kinase C, in particular the diacylglycerol known as "dioctanoyl glycerol." (see, e.g., Johnston et al., EXPERIMENTAL CELL RESEARCH 201,91-98 (1992), in particular page 91, 1st paragraph of Methods. Note that Johnston further teaches "dioctanoyl glycerol," referred to throughout Johnston as "DOG," can be purchased from Sigma in the column bridging paragraph on page 92). Moreover, as evidenced by the teachings of Rider et al., J Immunol. 1988 Jan 1;140(1):200-7, the term "dioctanoylglycerol" was used in the art as short-hand for "sn-1,2-dioctanoylglycerol," and as further evidenced by the Sigma product sheet for "1,2-Dioctanoyl-sn-glycerol" one synonym is "DOG".

Thus, applicant's argument that the claimed method does not encompass in its breadth the inclusion of protein kinase C activating compounds amounts to arguing a limitation not claimed. Moreover, as taught by Darfler interleukin-2 itself is capable of activating protein kinase C (see page 5, 2nd paragraph).

Lastly, with respect to applicant's argument regarding Cardarelli teaching an effect of fibronectin on T cell proliferation but not cytotoxicity, this is not found convincing for several reasons.

First, Cardarelli need not explicitly teach anti-CD3 + fibronectin + IL-2 produces cytotoxic lymphocytes from peripheral mononuclear cells to make the production of cytotoxic lymphocytes in the presence of fibronectin obvious.

Rather, the teachings of Cardarelli that the addition of immobilized fibronectin and IL-2 to HPBL cultures stimulated with anti-CD3 in the presence of serum-free media enhances HPBL proliferation (see Figure 1), and further that anti-CD3 and fibronectin, without added IL-2, induce expression of CD25, a crucial component for IL-2 induced T cell activation, and display "an increased light scatter profile characteristic of an activated phenotype," (see 1st paragraph of Discussion on pages 113-114) would be sufficient to motivate one of ordinary skill in the art to include fibronectin in a method of making cytotoxic T cells from peripheral mononuclear cells. This is because the skilled artisan would have a reasonable expectation that peripheral mononuclear cells expanded in the presence of anti-CD3 + fibronectin + IL-2 would not only be expanded to large numbers but would also be fully sensitive to the LAK-inducing effects of IL-2 via binding of IL-2 to CD25.

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

9. Claims 20 and 21 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Frederick Darfler (WO 88/02774) in view of Ochoa et al. (Cancer Res. 1989 Feb 15;49(4):963-8), Cardarelli et al. (Cell Immunol. 1991 Jun;135(1):105-17, cited on an IDS) and Taguchi et al. (U.S. Patent 5,198,423, cited on an IDS) as applied to claims 1-4, 6-9, 13, 15 and 16 above, and further in view of Chen et al. (J Immunol. 1994 Oct 15;153(8):3630-8, cited on an IDS), essentially for the reasons of record as put forth in the Office Action mailed July 12, 2010.

Applicant argues the instant claims are allegedly non-obvious for the same reasons that claims 1-4, 6-9, 13, 15 and 16 are allegedly non-obvious.

Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed July 12, 2010 as described in the preceding section.

10. Claims 1-4, 6-9, 13, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sagawa et al. (WO 03/016511, cited on an IDS) in view of Johnson et al. (J Immunol. 1992 Jan 1;148(1):63-71, cited on an IDS), Frederick Darfler (WO 88/02774) and Animal Cell Culture, a practical approach (RI Freshney ed., IRL Press, 1986, pp 26-41, cited on an IDS), as evidenced by the teachings of Sagawa et al. (US 2005/0042208, cited on an IDS) which is the U.S. National Stage Application based on Sagawa WO 03/016511 as well as Mazumder et al. (Cancer. 1984 Feb 15;53(4):896-905).

As a preliminary matter, it is noted that the teachings of Sagawa '511 are put forth in the context of the English language U.S. National Stage entry of the '511 international application, the Sagawa US 2005/0042208 publication. Nonetheless, Sagawa '511 is applied as a 102(b)/103 type reference.

Sagawa teaches a method for preparing a cytotoxic lymphocyte comprising culturing peripheral mononuclear cells in the presence of a plate bound fibronectin fragment represented by SEQ ID NO: 13 (see, e.g., pages 8-9, paragraph [0122]-[0137] and Example 12 on page 27). Sagawa also teaches the cell densities and culturing steps of the instant claims, see, ibid.

While Sagawa teaches their method is not limited to any particular medium (see paragraph [0128]) it does not explicitly teach the use of serum-free medium.

However, as taught by Darfler it was common knowledge in the art when making cells for use in adoptive immunotherapy, serum-free media is advantageous because of the extreme cost of sera, its limited availability and the possibility that it might be contaminated by microorganisms, especially viruses (see page 3, 1st paragraph).

With this common knowledge in the art in mind, it would have been obvious to one of ordinary skill in the art, and one of ordinary skill in the art would have been motivated to

make use of either a low serum or a serum-free media as taught by Darfler to carry out the method of Sagawa.

Moreover one of ordinary skill in the art would have had a reasonable expectation of successfully practicing the method of Sagawa in no or low serum medium.

In particular, Darfler teaches that when it comes to culturing peripheral mononuclear cells in the presence of IL-2 and no serum medium, if the appropriate no-serum medium is used the cytotoxicity of the cultured cells is nearly identical to growth in serum containing medium (see Darfler Example III). Note that the "PBL cells" of Darfler are actually peripheral mononuclear cells purified as described in Mazumder, see page 897, left col., 2nd and 3rd paragraphs and page 903, left col., 2nd paragraph, and as further evidenced by the teachings of Wolf et al., Vox Sang. 2005 May;88(4):249-55, see, e.g., Introduction; page 251-52, "Resulting Products" and Table 3.

Likewise, as taught by Johnson isolated T cells grown in the presence of serum-free medium, sepahrose bound-anti-CD3 and IL-2 reach maximal proliferation levels equivalent to growth in medium + 10% FCS (see Table 1).

Furthermore, low or no-serum media was commonly used in the art of mammalian cell culture as taught by Freshney (see entire document).

Thus, given the teachings of Darfler, Freshney and Johnson one of ordinary skill in the art would have had a reasonable expectation of successfully practicing the method of Sagawa in no or low serum medium.

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant puts forth the following argument on pages 13-14 of their remarks:

"Sagawa teaches that cytotoxic lymphocytes are induced in the presence of a fibronectin fragment in a serum-containing medium. Sagawa's method, however, also employs an antigen presenting cell as an essential element. Applicants note that the claimed method does not require an antigen presenting cell. Accordingly, the claimed method is completely different from Sagawa. Applicants further note that Darfler teaches that LAK cells are induced by adding a compound for activating kinase C in a serum-free medium, which is also not necessary to the instantly claimed method.

Applicants submit that one of ordinary skill in the art would not have the proper rationale or have been motivated to combine Sagawa with Darfler. Due to the different essential elements

described in Sagawa and Darfler, an ordinary artisan could not have been reasonably certain that merely substituting the serum-containing medium of Sagawa with the serum free medium of Darfler would have predictably resulted in cytotoxic lymphocyte induction from the naive T cells described in Sagawa.

Johnson and Freshney fail to remedy this unpredictability. Johnson describes isolated T cells, not the naive T cells described in Sagawa. Freshney merely describes that serum-free medium is used in the general culture of animal ceils, and never suggests the induction of cytotoxic lymphocytes using a serum-free medium. Accordingly, an ordinary artisan would not have the proper rationale or have been motivated to combine the methods of Johnson and Freshney with those of Sagawa.

Applicants further note that the present claims describe peripheral mononuclear cells or umbilical cord blood mononuclear cells. In contrast, Johnson describes isolated T cells. Accordingly, the starting material described in the claimed invention differs from that of Johnson."

Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed July 12, 2010.

First, as to applicant's argument that "the claimed method does not require an antigen presenting cell. Accordingly, the claimed method is completely different from Sagawa," the examiner agrees that the claimed methods do not require an antigen presenting cell; however, the claimed methods given their broadest reasonable interpretation consistent with the instant specification do encompass such an embodiment in their breadth, see, e.g., page 37-38 bridging paragraph to page 39, 1st paragraph.

Moreover, it is noted that peripheral mononuclear cells, a required element of the claimed invention, contain antigen-presenting cells, such as monocytes and B-cells.

Secondly, the examiner disagrees with applicant's assertion that the presence of an antigen presenting cell is an essential element of Sagawa's method. Some embodiments of Sagawa do not require an antigen-presenting cell, e.g., Sagawa teaches methods for maintaining cytotoxic T cells having antigen-specific cytotoxic activity, or expanding cytotoxic T cells having antigen-specific cytotoxic activity comprising culturing said cells in the presence of a plate bound fibronectin fragment represented by SEQ ID NO: 13 (see, e.g., Sagawa at pages 2-3, paragraphs [0029]-[0048] ; Example 12 on page 27 and claims 8-24).

In conclusion, in contrast to applicant's argument, the only substantive difference between the teachings of Sagawa and the claimed invention is that while Sagawa teaches their method is not limited to any particular medium (see Sagawa paragraph [0128]) it does not explicitly teach the use of serum-free medium.

Applicant further argues "Darfler teaches that LAK cells are induced by adding a compound for activating kinase C in a serum-free medium, which is also not necessary to the instantly claimed method" and applicant insinuates the presence of a compound for activating kinase C in the serum-free medium of Darfler is an "essential element" of the Darfler method which allegedly distinguishes it from the claimed method.

These arguments are also not convincing for several reasons. First, while Darfler teaches producing LAK cells in serum-free medium containing a non-proteinaceous compound for activating protein kinase C is nearly as efficient (97%) as producing LAK cells in serum-containing medium, Darfler nonetheless shows that medium lacking a non-proteinaceous compound for activating kinase C, but containing IL-2, which itself has the ability to activate kinase C, does produce LAK cells, albeit at lesser efficiency (see Darfler Example III and page 5, 2nd paragraph).

Secondly, while the examiner does not disagree that the claimed methods as currently presented do not require the presence a compound for activating kinase C, the claimed methods given their broadest reasonable interpretation consistent with the instant specification do encompass such an embodiment in their breadth.

In particular, objective evidence teaches that the AIM-V serum-free medium used in applicant's working examples contains the protein kinase C activating compound "dioctanoyl glycerol." (see, e.g., Johnston et al., EXPERIMENTAL CELL RESEARCH 201,91-98 (1992), in particular page 91, 1st paragraph of Methods. Note that Johnston further teaches "dioctanoyl glycerol," referred to throughout Johnston as "DOG," can be purchased from Sigma in the column bridging paragraph on page 92). Moreover, as evidenced by the teachings of Rider et al., J Immunol. 1988 Jan 1;140(1):200-7, the term "dioctanoylglycerol" was used in the art as short-hand for "sn-1,2-dioctanoylglycerol," and as further evidenced by the Sigma product sheet for "1,2-Dioctanoyl-sn-glycerol" one synonym is "DOG".

Furthermore, all of the working examples put forth in the instant specification include IL-2, and as taught by Darfler (see, ibid), IL-2 itself is capable of activating protein kinase C.

As to applicant's argument that "Johnson describes isolated T cells, not the naive T cells described in Sagawa" it is not clear why applicant draws this distinction because the isolated T cells of Johnson do contain both activated and naive T cells given that they were isolated from peripheral mononuclear cells by virtue of CD2 positive selection, i.e., by their ability to bind to neuraminidase-treated sheep red blood cells.

In conclusion, the claimed invention is obvious in view of the cited references because the teachings of the Darfler establish that one of ordinary skill in the art would have been motivated to perform the method of Sagawa using serum free medium (see above), and furthermore given the teachings of Darfler, Johnson and Freshley that the use of such medium would have been reasonably expected to successfully produce cytotoxic

lymphocytes when combined with the method of making cytotoxic lymphocytes described by Sagawa.

Claims 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sagawa et al. (WO 03/016511, cited on an IDS) in view of Johnson et al. (J Immunol. 1992 Jan 1;148(1):63-71, cited on an IDS), Frederick Darfler (WO 88/02774) and Animal Cell Culture, a practical approach (RI Freshney ed., IRL Press, 1986, pp 26-41, cited on an IDS), as evidenced by the teachings of Sagawa et al. (US 2005/0042208) which is the U.S. National Stage Application based on Sagawa WO 03/016511 as well as Mazumder et al. (Cancer. 1984 Feb 15;53(4):896-905), as applied to claims 1-4, 6-9, 13, 15 and 16 above, and further in view of Chen et al. (J Immunol. 1994 Oct 15;153(8):3630-8, cited on an IDS).

The combined teachings of Sagawa, Johnson, Darfler and Freshney are described above.

They do not teach transducing a foreign gene into the T cells.

Chen teach that retroviral transduction of T cells with PKC allows long term growth of the cells in vitro with maintenance of function and specificity, thus providing a useful approach for more easily procuring large numbers of said cells (see pages 3634-3635, in particular).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to further transduce the cytotoxic T lymphocytes made by the method of Sagawa, Johnson, Darfler and Freshney with a retrovirus encoding PKC as taught by Chen. One of ordinary skill in the art at the time the invention was made would have been motivated to do so, and have a reasonable expectation of success, since Chen et al. teach that retroviral transduction of T cells with PKC allows long term growth of the cells in vitro with maintenance of function and specificity, thus providing a useful approach for more easily procuring large numbers of said cells.

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant argues the instant claims are allegedly non-obvious for the same reasons that claims 1-4, 6-9, 13, 15 and 16 are allegedly non-obvious.

Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed July 12, 2010 as described in the preceding section.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1-4, 6-9, 13, 15, 16, 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Parker et al. (Hum Gene Ther. 2000 Nov 20;11(17):2377-87) in view of Bagnis et al. (WO 99/05301, cited on an IDS) as evidenced by Bagnis et al. (6,287,864, cited on an IDS) which the English language U.S. National Stage entry of WO 99/05301, and as further evidenced by the Gibco/Invitrogen Publication "A Guide to Serum-Free Cell Culture," 2003, pages 1-7 as well as Kaldjian et al. J Immunol Methods. 1992 Mar 4;147(2):189-95.

As a preliminary matter, it is noted that the teachings of Bagnis '301 are put forth in the context of the English language U.S. National Stage entry of the '301 international application, the Bagnis 6,287,864 patent.

Parker teaches a method for preparing a cytotoxic lymphocyte comprising culturing peripheral mononuclear cells in AIM V medium + IL-2 + anti-CD3 antibody for 3 days, harvesting the cells by centrifugation and resuspending with a retroviral supernatant in the presence of added IL-2 on a tissue culture plate, followed by culturing until day 4 on said tissue culture plate, refreshing the retroviral supernatant and IL-2 and culturing until day 5 on said tissue culture plate, then removing most of the retroviral supernatant and replacing it with culture medium containing IL-2 and culturing on said tissue culture plate until cellular harvesting on day 6 or 7. (see paragraph bridging pages 2378-79). Note that as evidenced by the Gibco/Invitrogen Publication as well as the teachings of Kaldjian, the AIM V medium used by Parker was a serum free medium (see page 5 of the Gibco/Invitrogen Publication and the Kaldjian Abstract).

Parker does not explicitly teach inclusion of a recombinant fibronectin fragment on the tissue culture plate in the method for preparing a cytotoxic lymphocytes.

However, Bagnis teaches the use of retroviral supernatant in serum-free medium and in the presence of an immobilized recombinant fibronectin fragment identical to SEQ ID NO: 13 of the instant specification (see attached alignment) for the transduction of mammalian cells including, e.g., non-adhesive low-density mononuclear cells, lymphoid mother cells, mature blood cells, lymphocytes, B cells, T cells (see entire document including, e.g., cols. 2, 7 and 8).

Given the reference teachings it would have been obvious to one of ordinary skill in the art, and one of ordinary skill in the art would have been motivated and have had a reasonable expectation of successfully modifying the method of making cytotoxic lymphocytes taught by Parker by using a retroviral supernatant prepared in a serum-free medium and further by

performing the transduction in the presence of immobilized recombinant fibronectin fragment as taught by Bagnis since the use of serum carries with it a number of disadvantages as taught by Bagnis at col. 2. Furthermore, even after removing most of the retroviral supernatant at day 5 as taught by Parker, it would have been obvious to continue culturing the transduced cells in serum free medium, such as AIM-V, given that this medium was used for the initial culturing during days 1-3 of Parker and further given the clinical advantages of growing cells in serum-free media, such as viral contamination and lot to lot variability as described by Bagnis.

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 1-4, 6-9, 13, 15, 16, 20 and 21 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 5-7, 10, 12, 28, 29, 31-35 and 37-39 of copending Application No. 10/509,055 (20050227354, cited on an IDS) in view of Johnson et al. (J Immunol. 1992 Jan 1;148(1):63-71, cited on an IDS), Frederick Darfler (WO 88/02774) and Animal Cell Culture, a practical approach (R1 Freshney ed., IRL Press, 1986, pp 26-41, cited on an IDS).

Applicant argues "As noted above, Applicants submit that an ordinary artisan could not have reasonably expected that the cytotoxicity of differentiated peripheral mononuclear cells or umbilical cord blood mononuclear cells could have been enhanced or a high cytotoxicity activity maintained by incubating the described precursor cells with a combination of recombinant fibronectin fragment and serum free medium in view of Johnson, Darfler and Freshney. See also Example 25, page 95 of the originally filed application, as noted above, which demonstrates the results of the claimed invention."

Applicant's argument is not found convincing for the reasons put forth in Section 10 above, in short because the teachings of the Darfler establish that one of ordinary skill in the art would have been motivated to perform the method of the reference claims using serum free medium (see above), and furthermore given the teachings of Darfler, Johnson and Freshley that the use of such medium would have been reasonably expected to successfully produce cytotoxic lymphocytes when combined with the method of the reference claims.

15. No claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARY SKELDING whose telephone number is (571)272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Phuong N. Huynh can be reached on 571-272-0846. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Zachary Skelding/
Primary Examiner, Art Unit 1644